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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,057	01/28/2004	Roy H. Larsen	50147/003002	2306

21559 7590 08/13/2008

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EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
08/13/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/766,057	LARSEN ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 25-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 25-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 18 and 25-35 are pending in the application. Any objections and/or rejections from previous office actions that have not been reiterated in this office action are obviated.

Response to Arguments

1. Applicant's arguments filed 5/29/08 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 18 and 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Sinkule et al. (EP 282057) as stated in the office action mailed 11/26/07.

4. Applicant asserts that the claims are directed to conjugates that contain two different targeting moieties: an antibody, antibody fragment, or antibody construct with affinity for a tumor-associated antigen, and a non-toxic folate. None of Niswender, Wedeking, and Sinkule teaches or suggests the use of two different targeting moieties in a single conjugate molecule.

5. The reference of Niswender teaches of a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof, 2.) an antibody, such as a gamma globulin (as evidenced by Wikipedia and not excluding human) and/or 3.) a radionuclide or radionuclides. Therefore the folic acid and antibody encompass the two different targeting moieties of the instant claims. The reference of Wedeking et al. teaches of a gadolinium-folate (folic acid) conjugate comprising multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium. It would have been obvious to one skilled in the art to couple the folate of Wedeking et al. to an antibody (Niswender) as both disclosures are drawn to folic acid conjugates containing radionuclides. It would be predictable to include an antibody into the conjugates of Wedeking et al. to provide for site-specific targeting as Sinkule et al. teaches that an antibody may be used for a wide variety of target antigens.

6. Applicant asserts that Niswender describes conjugates that contain a folic acid moiety conjugated to a stabilizing protein radical (e.g., rabbit gamma globulin). Neither the folic acid moiety nor the stabilizing protein radical in the Niswender conjugates are described for their function in targeting a cell or binding a cell *in vivo*. Thus, Niswender clearly does not teach or suggest a combination of two different *targeting* moieties.

7. The reference of Sinkule et al. was used to teach that an antibody may be used for a wide variety of target antigens. The reference of Niswender was used to teach of a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof, 2.) an antibody, such as a gamma globulin (as evidenced by Wikipedia and not excluding human) and/or 3.) a radionuclide or

radionuclides. Therefore the folic acid and antibody encompass the two different targeting moieties of the instant claims and are capable of the same functions. The reference of Wedeking et al. was used to teach of a gadolinium-folate (folic acid) conjugate comprising multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium. It would have been obvious to one skilled in the art to couple the folate of Wedeking et al. to an antibody (Niswender) as both disclosures are drawn to folic acid conjugates containing radionuclides. It would be predictable to include an antibody into the conjugates of Wedeking et al. to provide for site-specific targeting as Sinkule et al. teaches that an antibody may be used for a wide variety of target antigens.

8. Applicant asserts that Wedeking et al. describes the use of folates and folic acid derivatives for cellular uptake and chemotherapy. Wedeking does not disclose a conjugate that contains both a folate or folic acid derivative *and* a tumor-specific antibody and, therefore, also fails to teach or suggest the combination of two different targeting moieties.

9. The reference of Wedeking et al. was not used to teach of the combination of two different targeting moieties (i.e.folate or folic acid derivative *and* a tumor-specific antibody) but was used to teach of a gadolinium-folate (folic acid) conjugate comprising multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium. The reference of Niswender was used to teach of a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof, 2.) an antibody, such as a gamma globulin (as evidenced by Wikipedia

and not excluding human) and/or 3.) a radionuclide or radionuclides. It would have been obvious to one skilled in the art to couple the folate of Wedeking et al. to an antibody as the disclosures of Niswender and Wedeking et al. are drawn to folic acid conjugates containing radionuclides.

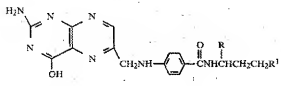
10. Applicant asserts that Sinkule teaches conjugates containing a tumor-specific antibody conjugated to a chemotherapeutic agent (e.g., a toxic folic acid analog). Sinkule does not suggest the replacement of the toxic folic acid analog with a non-toxic folic acid.

11. The reference of Sinkule et al. was not used to teach of replacing of the toxic folic acid with a non-toxic folic acid. Sinkule et al. was used to teach that an antibody may be used as a target entity.

12. Applicants point out to the Office that the chemical formula disclosed in Niswender does not encompass or suggest the claimed conjugates. In the formula disclosed in Niswender (column 1, lines 19-25), a carboxy radical, a protein radical (-C(=O)-NH-R^3), and a cyclic radical of formula A are alternatives for the R and R' positions, providing that at least one of R or R' is a carboxy, or a salt or amide thereof. Thus, because one group must be taken by the carboxy alternative, only one position remains, which can accommodate either a protein radical, such as gamma globulin, or a cyclic radical A, which may then be radiolabeled.

13. The formula of Niswender (formula I, below) states that R and R^1 are carboxy, a radical of the formula (-C(=O)-NH-R^3), where NH-R^3 is a protein radical derived from gamma globulin or a radical (formula II) where X is a radionuclide. Therefore at least

one site R or R^1 may comprise a gamma globulin and the other site may comprise a radionuclide which encompasses the instant claims of one antibody, antibody construct and a folate coupled to a radionuclide.

14.  I  II

15. In view of the reference of Wedeking et al. which teaches of the gadolinium-folate (folic acid) conjugate comprising multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium, it would have been obvious to one skilled in the art to replace the radical of formula II above (Niswender) with a chelate capable of binding gadolinium since the disclosures of Niswender and Wedeking et al. are drawn to folic acid conjugates containing radionuclides

16. Applicant asserts that the disclosure of Niswender, Wedeking, and Sinkule are directed to disparate uses, which necessarily require different properties, Applicants submit that prior to the present invention, a skilled artisan would not have been motivated to combine Niswender, Wedeking, and Sinkule to arrive at the Applicants' invention.

17. The references of Niswender, Wedeking et al., and Sinkule et al. are drawn to conjugates comprising folate/folic acid coupled to a radionuclide. The references of Wedeking et al. and Sinkule et al. further teach coupling the folate/folic acid to an antibody for targeting (Sinkule et al.). The references do not need to be drawn to the same use of the conjugates or to solve the same problem of the instant claims.

18. Claims 18,25-28 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niswender (US 4,336,185) in view of Wedeking et al. (US 6,093,382) and further in view of Goldenberg et al. (US 5,698,178) as stated in the office action mailed 11/26/07.

19. Applicant assert that Goldenberg does not teach or suggest conjugates having: (I) an antibody, an antibody fragment, or antibody construct with affinity for a tumor-associated antigen, and (2) a non-toxic folate. Furthermore, a skilled artisan would not be motivated to substitute the toxic folic acid analog disclosed in Goldenberg with a non-toxic folic acid, as such substitution would reduce the chemotherapeutic function of the conjugates.

20. The reference of Goldenberg was used to teach of receptor binding conjugates comprise various targeting antibodies and at least one diagnostic or therapeutic agent (such as radionuclides and folic acid analogues). The antibodies that may be used as the targeting antibody which provides for the clearance of a nontargeted circulating radiolabeled antibody are IgG and IgM. The reference of Niswender teaches of a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof, 2.) an antibody, such as a gamma globulin (as evidenced by Wikipedia and not excluding human) and/or 3.) a radionuclide or radionuclides. The reference of Wedeking et al. teaches of a gadolinium-folate (folic acid) conjugate comprising multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium. It would have been obvious to one skilled in the art to couple the

folate of Wedeking et al. to an antibody as the disclosures of Niswender and Wedeking et al. are drawn to folic acid conjugates containing radionuclides. It would have been predictable for one skilled in the art to substitute the antibodies of Goldenberg for the antibodies of the conjugates of the combined disclosures of Niswender and Wedeking to provide for targeting of the conjugates.

Conclusion

No claims are allowed at this time.

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618